connection with filing this paper, if the attached check is improper, in the wrong amount, or missing, or with this application or the parent application during their entire pendency, may be charged to Deposit Account No. 50-1213.

This paper is responsive to the Office Action, mailed January 30, 2001. A prior Office Action had alleged that a prior response was non-responsive because the claims were alleged to have been amended to read on non-elected subject matter, group III. In response, a CPA divisional application was filed so that the claims deemed non-elected and deemed to be part of group III would be examined. In response, the Office, examined only amended claims 19-24 and did not examine the remaining claims 32-36 and 38 in group III. In a telephonic interview the Examiner, who is thanked for his courtesy in conducting the interview, explained that claims 19-24 were distinct from claims of group III, and hence, the remaining claims in group III were not examined.

To avoid such confusion in connection with this second filing of CPA divisional, claims 19-24 are cancelled herein. The presently pending claims constitute groups III and VI, which as urged below should be rejoined.

If the Restriction Requirement as between groups III and VI is maintained, examination of group III, claims 10-18, on the merits is respectfully requested. Claims 10-24, 32-36, 38 and 41 are presently pending in this application. Claims 32-36, 38, 41 and 42 are retained to provide the Office an opportunity to reconsider the propriety of the restriction requirement.

As discussed previously if the requirement as between groups III and VI is maintained, the Office is precluded from holding obviousness-type double patenting as between applications and patents that each claim the subject matter of one of these groups. Applicant reserves the right to file divisional applications to the non-elected subject matter.

REQUIREMENT FOR RESTRICTION

The Restriction Requirement is traversed as between Groups II, III and IV. It is noted that Group III, claims 10-18, is directed to methods of improving treatment outcome or reducing risk of treatment by assessing treatment options for a particular disease or condition, measuring cell activation levels, and if, elevated, administering cell activation lowering therapy; and Group VI, claims 32-36, 38 and 41, is directed to methods of diagnosis and treatment by assessing cell activation, and if elevated, administering cell activation lowering therapy. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Since, if restriction is required by the Office double patenting cannot be held, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

If the requirement is maintained, applicant can obtain two patents: one directed to methods of improving treatment outcome or reducing risk of by assessing treatment options for a disease, measuring cell activation and, if elevated, administering cell activation lowering therapy (group III); and a second directed to methods of diagnosis and treatment by measuring cell activation and then, if it is elevated, administering cell activation lowering therapy (group VI). If, for example, claims to group III issue first, the Office will be precluded from holding obviousness-type double patenting as between the first issuing patent with claims that includes the steps of assessing treatment options, assessing

cell activation and then administering cell activation lowering therapy, and a later issuing patent with claims that include the steps of assessing cell activation and then administering cell activation lowering therapy.

THE REJECTION OF CLAIMS 19-24 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 19-24 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. It is respectfully submitted that this ground for rejection is rendered moot by virtue of cancellation of claims 19-24.

THE REJECTION OF CLAIMS 19-24 UNDER 35 U.S.C. §103(a)

Claims 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada *et al.* ((1991) *Journal of International Medical Research 19*:348-350) and Okada *et al.* ((1991) *Journal of International Medical Research 19*:234-236) because these references allegedly teach treatment of diabetes with a protease inhibitor, and the first Okada *et al.* reference allegedly teaches administer futhan with insulin. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to have administered the protease inhibitor before administering insulin. This rejection is respectfully traversed insofar as it is applicable to any of the pending claims.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have

suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. In re Sernaker, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The claims

Claim 10 is directed to a method of improving treatment outcome or reducing risk of treatment by assessing treatment options, measuring cell activation levels in a subject; and, if elevated, administering activation lowering

therapy prior to commencing any further treatment for the disease or condition. Dependent claims specify the methods for assessing cell activation, the diseases and conditions for which treatment is assessed, and the cell activation lowering therapy.

Claim 32 is directed to a method of diagnosis and treatment by assessing cell activation; and, if elevated, administering activation lowering therapy. Dependent claims specify that the treatment is administration of a protease inhibitor, and that the protease inhibitor is a serine protease. Dependent claims also specify methods for assessing cell activation.

Differences between the claims and the disclosure of the cited reference

Okada *et al.*

Okada *et al.* ((1991) *Journal of International Medical Research 19*:234-236)

Okada *et al.* teaches that Futhan inhibits complement activation associated with islet cell surface antibody in children with insulin-dependent diabetes mellitus soon after the onset of the disease.

Okada *et al.* ((1991) *Journal of International Medical Research 19*:348-350)

Okada *et al.* presents a study of the effect of Futhan on complement activation in an adult male with insulin-dependent diabetes mellitus and provides further evidence of complement activation in insulin-dependent diabetes mellitus.

Thus, the Okada *et al.* references teach that complement activation is involved in insulin-dependent diabetes mellitus; and the first Okada *et al.* reference also teaches that Futhan is an inhibitor of complement activation.

Neither Okada *et al.* reference, singly or in combination teaches or suggests that futhan lowers the levels of cell activation or a method of treatment or diagnosis that includes the step of measuring the level of cell activation, and, if it is elevated, administering cell activation lowering therapy.

Analysis

The combination of teachings of the cited references does not result in the instantly claimed methods

As described in the application cell activation refers to changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces. The application teaches that levels of cell activation are predictive of responsiveness to certain treatments and outcomes of certain treatments. Hence the application and claims are directed to methods in which levels of cell activation are assessed to determine whether or not to treat for disease, and, if the levels are high to initiate cella activation lowering therapy as way to improve treatment outcomes.

Neither Okada *et al.* reference teaches or suggests a method for reducing cell activation nor that administering cell activation lowering therapy prior to administering treatment for a particular disease or disorder has any effect on treatment outcomes or treatments for a particular disorder. Thus, neither reference, singly or in combination, teaches or suggests the steps of assessing cell activation level, and, administering a treatment to lower cell activation level before commencing any other treatment. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 19-24 are also rejected as being unpatentable over Yanamoto *et al.* or Yonekura *et al.* or Murohara *et al.* in view of Okada *et al.* because each of Yanamoto *et al.* or Yonekura *et al.* and Murohara *et al.* allegedly teach administering protease inhibitor for treating disorders in combination with

treatment for the condition. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to have "add[ed] a protease inhibitor immediately before treatment" because whether it is administered before or during treatment is a matter of obvious design choice (no reference is provided to evidence the latter premise). This rejection is respectfully traversed.

The claims and relevant law are discussed above.

Yanamoto *et al.*

Yanamoto *et al.* reports the therapeutic effect of Futhan for treating cerebral vasospasm. Yanamoto *et al.* does not disclose or suggest that Futhan is effective for lowering cell activation, nor does no Yanamoto *et al.* disclose or suggest a method for improving outcome or treatment of a disorder or lowering the risk of developing the disorder by lowering cell activation by administering a protease inhibitor.

Yanamoto *et al.* does not teach or suggest a method of treatment or diagnosis in which the level of cell activation is measured prior to administering any treatment for a disorder, and if the level is high, administering cell activation lowering treatment.

Yonekura *et al.*

Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with nafamostat mesylate (Futhan). Yonekura *et al.* discloses that Futhan inhibits proteinases of the coagulation, fibrinolysis, Kallkrein kinin and complement systems.

The reference does not teach the use of Futhan or any protease inhibitor for lowering cell activation nor for a method of treatment or diagnosis in which the level of cell activation is measured prior to administering any treatment for a disorder, and if the level is high, administering cell activation lowering treatment.

Morohara *et al.*

Morohara *et al.* describes a study that assesses the *in vivo* effects of a protease inhibitor on myocardial tissue necrosis and neutrophil accumulation in a rat model of myocardial infarction/reperfusion injury. The reference does not teach or suggest a method of treatment or diagnosis in which the level of cell activation is measured prior to administering any treatment for a disorder, and if the level is high, administering cell activation lowering treatment.

Analysis

The combination of teachings of the cited references does not result in the instantly claimed methods

None of the cited references, singly or in any combination thereof, teaches or suggest any method of treatment or diagnosis in which the level of cell activation is assessed, and if it is elevated, cell activation therapy is administered prior to administration of any other therapy.

As taught in the application, many of the varied and unpredictable outcomes to treatment in acute and chronic disease, is related to the level of cell activation. It is this parameter that explains what had heretofore seemed unpredictable. The methods claimed in this application provide a means to predict to whom and when to administer treatment. By assessing the levels of cell activation, the clinician can determine, for example, whether surgery should be performed or whether other treatment should be administered, based upon the level of cell activation that a patient presents. If the level is high, cell activation lowering therapy can be initiated prior to other treatments. If it is low, then treatment options can be selected accordingly.

None of the references of record, singly or in any combination thereof, teaches or suggests a relationship between the levels of cell activation and the timing and type of the treatment to administer, nor do the references teach or suggest that treatment outcome can be improved if cell activation levels are tested and lowered prior to initiating treatment. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above, examination and allowance of the application are respectfully requested.

Respectfully submitted,
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